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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 5, 1943

SOME THEORETICAL CONSIDERATIONS CONCERNING THE INTERCHANGE OF METABOLITES BETWEEN CAPILLARIES AND TISSUE

INGRAM BLOCH
THE UNIVERSITY OF CHICAGO

The author's previous treatment of diffusion of oxygen from an idealized capillary is made more exact; the treatment here is valid for any substance which diffuses between blood and tissue, though the physical situation is still somewhat idealized. A general equation is derived but not solved.

Then follows an approximate treatment of the case in which all capillaries within a certain sphere have ceased to flow; conditions are discussed under which cells at the center of this sphere will die.

In an earlier paper (Bloch, 1941), the author presented an approximate treatment of the problem of diffusion of oxygen from a capillary. The present paper contains a formulation of the exact problem of diffusion of any substance from or into a capillary.

We shall again consider a circular cylindrical capillary of length l, whose axis is to be the ζ-axis, so that $\zeta = 0$ at the arteriole and $\zeta = l$, at the venule. $r(P)$ will be the distance of point P in the tissue from the ζ-axis; r_0 will be the radius of the capillary, and v the velocity of the blood-flow. D and h will denote, respectively, the tissue diffusion coefficient and the capillary permeability of the substance under consideration, while $Q(P)$ will be the rate of production of the substance in gm/cc sec at point P in the tissue. r_o and h are assumed to be constant.

I. The case of oxygen: For consideration of oxygen, we shall need to define some more quantities:

$c_o(\zeta) =$ concentration, in gm cm^{-3}, of oxygen dissolved in the blood.

$c_1 = c_o(0)$, $c_2 = c_o(l)$, $c'(\zeta) =$ concentration, in gm cm^{-3}, of oxygen in the tissue immediately outside the capillary wall.

$x_o(\zeta) =$ concentration, in gm per cm^3 of blood, of removable oxygen in oxyhemoglobin.

$x_1 = x_0(0)$, $x_2 = x_0(l)$, $T_0(\zeta) = x_0(\zeta) + c_0(\zeta)$, $T_1 = x_1 + c_1$, $T_2 = x_2 + c_2$, $c(P) =$ concentration, in gm cm^{-3}, of oxygen at point P in the tissue.

$$\sigma = -\frac{1}{4\pi}\left(\frac{\partial c}{\partial r}\right)_{r=r_0}. \tag{1}$$

From material balance (Bloch, 1941), we have the following expression:

$$-vr_0\frac{dT_0}{d\zeta} = 2h[c_0(\zeta) - c'(\zeta)] = 8\pi D\sigma. \tag{2}$$

Also we know that the diffusion equation may be used in the tissue:

$$\nabla^2 c = -\frac{Q}{D}.$$

The diffusion equation may be otherwise stated; the capillaries in the volume V' of tissue will make a contribution to $c(P)$ which will be given by the sum of several surface integrals, each of which is taken over the surface of one capillary; added to this sum will be a volume integral, which represents the effect of tissue metabolism within volume V':

$$c(P) = \sum_{i \text{ in } V'}\left\{\int\int_{S_i}\frac{\sigma(\zeta_i)\,dS_i}{\rho(p_i,P)}\right\} + \int\int\int_{V'}\frac{Q(P')\,dV'}{4\pi D\rho'(P',P)}. \tag{3}$$

Here S_i is the surface of the i-th capillary: $\rho(p_i,P)$ is the distance from P to p_i, the general point on S_i, and $\rho'(P',P)$ is the distance from P to P', the general point in V'. Equation (3) is a special case of the general solution of Poisson's equation (MacMillan, 1936).

Bloch (1941) gave a brief discussion of the effect of other capillaries on concentration of a metabolite at a point in the region of supply of some particular capillary. The only conclusion reached was that, in general, this effect could not be neglected. It will, however, be evident that distant capillaries will have less effect at points immediately outside the surface of some particular capillary than at points nearer the boundary of the region of supply. Hence, we shall set up equation (3) for $c'(z)$, and shall neglect all terms but the first in the summation. The z-axis is to be taken coincident with the ζ-axis, but whereas ζ is defined only for points within the capillary and on its surface, z is defined only for points in the tissue. Thus $c'(\zeta)$ and $c'(z)$ are logically distinct, but physically identical.

Equation (2), combined with equation (3) set up as proposed above, will still require one more relation to make the problem determinate. This relation may be most conveniently obtained by consideration of the equilibrium between dissolved oxygen and oxyhemoglobin, which consideration should lead us to an expression for $x_o(c_o)$.

$x_o(c_o)$ having been found, equation (3) for $c'(z)$ can be solved, and the quantities $c'(\zeta)$, $c_o(\zeta)$, $x_o(\zeta)$, $T_o(\zeta)$, and $\sigma(\zeta)$ will all be determined. Then this value of $\sigma(\zeta)$ can be substituted in each term of equation (3), which substitution, combined with a reasonable assumption about $Q(P)$, will reduce the problem of determining $c(P)$ in the field of n equivalent capillaries to that of evaluating the integrals. If, on the other hand, we prefer not to make any assumptions about $Q(P)$, we can use H. D. Landahl's expression for $Q(c)$ (Rashevsky, 1940) in the volume integral, in which case $c(P)$ will be the solution of an integral equation. Thus, by the use only of the approximation involved in dropping all but one of the terms in the summation in equation (3) when solving for $c'(z)$, we shall be able, in principle, to obtain an expression for $c(P)$.

Bloch (1941) gives a discussion of the equilibrium between oxygen and oxyhemoglobin, in which it is pointed out that x_o will depend not only on c_o, but also on concentration of CO_2 and on the time lag in dissociation of oxyhemoglobin. It has seemed expedient to neglect the time lag, and to determine the relationship between x_o and c_o and CO_2 concentration by reference to data in L. J. Henderson, (1928, p. 130). The curves here show y, percentage of hemoglobin oxidized, as a function of u, pressure of dissolved oxygen in millimeters of mercury. The parameter of the family of curves is w, pressure of CO_2; since its effect is slight (if w and u are expressed in mm Hg $(du/dw)_y \cong 1/4$ per cent mm^{-1} $(dy/dw)_u \cong 2/3$ per cent mm^{-1}), we have set $y(u,w) = y(u, \text{average } w)$. $y(u)$ may be fairly well represented in the significant range of u (from 20 to 80 *mm*) by a parabola:

$$y = \alpha_2 u^2 + \alpha_1 u + \alpha_0$$

where $\alpha_2 = -2.18 \times 10^{-2}$, $\alpha_1 = 3.24$, and $\alpha_0 = -27.3$.

To get $x_o(c_o)$, one must get $x_o(y)$ and $u(c_o)$. Both these relationships are simple proportionalities.

$$x_0 = \frac{x_s}{100} y = My \tag{4}$$

where x_s is the concentration of oxygen in HbO_2 (gm cm^{-3} of blood) when Hb is 100% oxidized, and $M \equiv x_s/100$.[1] Also, u is proportional to c_o:

$$u = Nc_0 .$$

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[1] It may be of interest here to note that anemia will be characterized by a low value of the quantity x_s. Perhaps in the future it will be possible to investigate anemia from this point of view.

Hence we have

$$x_0 = My = M(\alpha_2 u^2 + \alpha_1 u + \alpha_0) = M(\alpha_2 N^2 c_0^2 + \alpha_1 N c_0 + \alpha_0). \qquad (5)$$

Since $T_0 = x_0 + c_0$,

$$T_0 = c_0 + M(\alpha_2 N^2 c_0^2 + \alpha_1 N c_0 + \alpha_0) = \gamma_2 c_0^2 + \gamma_1 c_0 + \gamma_0 \qquad (6)$$

the γ's being defined in terms of the α's and N by equation (6).

Now we are able to combine equations (2), (3) and (6) into a single equation in one unknown.

First, since we shall be manipulating only the surface integral in equation (3), we shall substitute A for the volume integral. We have

$$c'(P) = \int_s\int \frac{\sigma(\zeta)\,dS}{\rho(p,P)} + A$$

or

$$c'(z) = \int_0^{2\pi} d\Theta \int_0^l \frac{r_0\sigma(\zeta)\,d\zeta}{\sqrt{2r_0^2(1-\cos\Theta) + (z-\zeta)^2}} + A \qquad (7)$$

where Θ is the angle between the radii vectores to the points p and P. Only one angle appears in the integrand because σ is assumed to be a function of ζ only.

From equation (2) we learn that

$$\sigma(\zeta) = -\frac{vr_0}{8\pi D}\frac{dT_0}{d\zeta} \qquad (8)$$

and that

$$c'(\zeta) = c_0(\zeta) + \frac{vr_0}{2h}\frac{dT_0}{d\zeta}. \qquad (9)$$

Equation (6) gives us another expression for $dT_0/d\zeta$:

$$\frac{dT_0}{d\zeta} = (2\gamma_2 c_0 + \gamma_1)\frac{dc_0}{d\zeta}. \qquad (10)$$

If we substitute in (8) and (9) the value of $dT_0/d\zeta$ given in (10), and substitute the resulting expressions for $c'(\zeta)$ and $\sigma(\zeta)$ in (7), we get

$$\begin{aligned} c_0(z) &+ \frac{vr_0}{2h}[2\gamma_2 c_0(z) + \gamma_1]\frac{dc_0}{dz} \\ &= \int_0^{2\pi} d\Theta \int_0^l -\frac{vr_0^2}{8\pi D}[2\gamma_2 c_0(\zeta) + \gamma_1]\frac{dc_0}{d\zeta} \\ &\times \frac{d\zeta}{\sqrt{2r_0^2(1-\cos\Theta) + (z-\zeta)^2}} + \int\int_{V'}\int \frac{Q(P')\,dV'}{4\pi D\rho'(P',P)}. \end{aligned} \qquad (11)$$

Equation (11) will, in principle, give us $c_0(\zeta)$, from which we can readily obtain $c'(\zeta)$, $\sigma(\zeta)$, $T_0(\zeta)$, and $x_0(\zeta)$. If we put the value of $\sigma(\zeta)$ thus derived into equation (3), we will have a determinate expression for $c(P)$. Therefore the present desideratum is the solution of (11). Unfortunately, however, equation (11) is of a form which is, so far as is known, not soluble. Hence we shall have to confine ourselves to an incomplete discussion of the solution.

First, it is evident that, since $O \leqq z \leqq l$, there will, for every choice of $P(z)$, be one point in the range of integration in (11) at which the integrand will become infinite. That this singularity will not make the integral become infinite can, however, be shown by the following argument: Consider a small circle, of radius δ, fitted to the surface of the capillary with its center at the point $P(z)$. If δ is sufficiently small; we may approximate the integration over the interior, η, of this circle by integration of a constant $\bar{\sigma}$, the average value of σ in the neighborhood of P, over a circular region of a plane; as δ approaches zero, this approximation becomes exact; for any $\delta > 0$, the singularity in the integrand occurs within the circle, so that there will be no singular points encountered in integrating over such of the capillary surface S as lies outside η. Now, if ε denotes the distance from the center of the circle to the general point in η, our integral becomes

$$\int_0^{\delta} \frac{\bar{\sigma} \cdot 2\pi\varepsilon}{\varepsilon}\, d\varepsilon = \int_0^{\delta} 2\pi\bar{\sigma}\, d\varepsilon = 2\pi\bar{\sigma}\delta .$$

This quantity obviously approaches zero as δ approaches zero, so that, as δ approaches zero, the integration over $S - \eta$ approaches a finite limit; it is evident that the singularity at P does not make the integral diverge.

II. The case of glucose: The problem of the diffusion of glucose is simpler than that of oxygen because glucose experiences no buffering so,

$$c_0(\zeta) \equiv T_0(\zeta), \quad x_0(\zeta) \equiv 0 .$$

For this reason, the equation corresponding to equation (11) is

$$c_0(z) + \frac{v r_0}{2h}\frac{dc_0}{dz} = \int_0^{2\pi} d\Theta \int_0^{l} \frac{-v r_0^2 \frac{dc_0}{d\zeta} d\zeta}{8\pi D\sqrt{2r_0^2(1-\cos\Theta)+(z-\zeta)^2}} + A. \quad (12)$$

The same argument as that given for the case of oxygen applies here and shows that the singularity in the integrand does not make the integral diverge.

III. Other cases: It will be seen that other metabolites will behave either like oxygen or like glucose; we shall denote the types of substances exhibiting these two types of behavior as types I and II, respectively, type II being, as we have seen, a special case of type I.

A. Non-buffered substances: All non-buffered substances behave like glucose, and hence belong to type II. Therefore equation (12) applies to their concentrations in the blood, and its solution will enable us to compute all other unknown quantities.

B. Buffered substances: In the general case of buffering, the substance will exist in several forms, in some of which, the "mobile" forms, it can pass through the capillary wall and in the rest of which, the "immobile" forms, it cannot. Let us denote by $c_0(\zeta)$ the total concentration, in gm per cc of blood, of the substance in mobile form, by $x_0(\zeta)$ its total concentration in immobile form, and, as for oxygen, by $T_0(\zeta)$ the sum $c_0(\zeta) + x_0(\zeta)$; let $c(P)$, $x(P)$, and $T(P)$ be the corresponding concentrations at point P in the tissue. Let us assume we know x as a function of c (x_0 as a function of c_0) when the forms are at equilibrium.

We are treating a steady state, so we assume the existence of equilibrium between mobile and immobile forms in the tissue, and, in accordance with the treatment of oxygen, neglect any time lag there may be in the transition between the two forms in the blood.

It will be seen that buffering in the tissue will manifest itself by influencing the production integral in equation (3). But, since we are dealing with the case in which exactly as much of the substance goes from the mobile form to the immobile form as goes the other way, at any point in the tissue, it is evident that buffering in the tissue has no effect on the value of Q, and hence introduces no change in our problem.

Buffering in the blood will manifest itself exactly as it did in our treatment of oxygen. σ will be defined in the same way, and equations (2), (3), and (7) will be unchanged. The steps between equation (7) and equation (11) will be essentially the same as before, except that, in general, we shall not have x_o as a function of c_o.

$$\frac{dT_0}{d\zeta} = \frac{d}{d\zeta}[x_0(c_0) + c_0] = \left[\frac{dx_0}{dc_0} + 1\right]\frac{dc_0}{d\zeta};$$

$\left[\frac{dx_0}{dc_0} + 1\right]$ will be known; let us denote it by $\phi(c_0)$. Hence, from equations (8) and (9)

$$\sigma(\zeta) = -\frac{vr_0}{8\pi D}\phi(c_0)\frac{dc_0}{d\zeta} \tag{13}$$

$$c'(\zeta) = c_0(\zeta) + \frac{vr_0}{2h}\phi(c_0)\frac{dc_0}{d\zeta}. \tag{14}$$

The generalized version of equation (11) will thus be

$$c_0(z) + \frac{vr_0}{2h}\phi(c_0)\frac{dc_0}{dz} = \int_0^{2\pi} d\Theta \int_0^{l} - \frac{vr_0^2}{8\pi D} \frac{\phi(c_0)\frac{dc_0}{d\zeta}\,d\zeta}{\sqrt{2r_0^2(1-\cos\Theta)+(z-\zeta)^2}} + A. \tag{15}$$

It will be evident that equations (12) and (14), for general substances of types II and I respectively, will hold whether the substances are being produced or consumed in the tissue, since the sign of Q does not affect the validity of equations (2), (3), or (7), from which the later equations are derived. Actually, also, equation (12) is a special case of equation (15), in which $\phi(c_0) \equiv 1$.

Thus the solution of equation (15) will determine the behavior of any metabolite in its passage between blood and tissue.

IV. Since the solution of equation (15) presents seemingly insurmountable difficulties, we shall derive an expression which should enable us to find, approximately, the effect of distant capillaries.

First, because we are interested in the concentration at a point far from a capillary, we shall treat the capillary as a line segment of length l, omitting the integration with respect to Θ in equation (3). In accordance with this change, we must replace σ, productivity per unit area, by λ, productivity per unit length. It will be seen that

$$\lambda = 2\pi r_0 \sigma. \tag{16}$$

Hence, if we denote by $c_i(P)$ the contribution to $c(P)$ made by the i-th capillary, and by $A(P)$ the effect at P of production in the tissue, as in equations (7), (12), (15), we have

$$c(P) = \sum_i c_i(P) + A(P). \tag{17}$$

The quantity $c_i(P)$ will be given by the following equation:

$$c_i(P) = \int_0^{l_i} \frac{\lambda(\zeta_1)\,d\zeta_i}{\rho(\zeta_i,P)} = 2\pi r_0 \int_0^{l_i} \frac{\sigma(\zeta_i)\,d\zeta_i}{\sqrt{r_i^2+(z_i-\zeta_i)^2}}. \tag{18}$$

Determination of $\sigma(\zeta)$ requires the solution of equation (15) or an equivalent equation, in which can not be used the line-segment approximation of this section, since the equation applies to a point adjoining the surface of the capillary. For this reason, we shall investigate the form of $c(P)$ for two simple forms of σ, assumed given.

From equation (2) we note that, if $\sigma(\zeta)$ is a polynomial of degree K, $T_0(\zeta)$ is a polynomial of degree $K+1$. In particular, if $\sigma(\zeta)$ is a constant, $\sigma(\zeta)=\sigma_0$, we have $T_0(\zeta)$ a linear function of ζ,

$$T_0(\zeta)=T_1+\frac{T_2-T_1}{l}\zeta$$

and (19)

$$\sigma=\sigma_0=\frac{vr_0}{8\pi D}\frac{T_1-T_2}{l}.$$

Also, if σ is linear, T_0 is quadratic:

$$T_0(\zeta)=T_0+\mu_1\zeta+\mu_2\zeta^2$$

and (20)

$$\sigma(\zeta)=-\frac{vr_0}{8\pi D}(\mu_1+2\mu_2\zeta)$$

In the case of quadratic $T_0(\zeta)$ [equation (20)], we have not enough facts at our disposal to evaluate the coefficients μ_1 and μ_2, but if $T_0(\zeta)$ is linear [equation (19)], all coefficients are determined. It will be seen later that this linear form is the most useful.

If $\sigma(\zeta)$ is constant, equation (19) tells us its value is $\dfrac{vr_0}{8\pi D}\dfrac{T_1-T_2}{l}$. Thus, from equation (18), we have, dropping the subscripts and performing the integration,

$$c(r,z)=\frac{vr_0^2(T_1-T_2)}{4Dl}\log\frac{\sqrt{r^2+(z-l)^2}+l-z}{\sqrt{r^2+z^2}-z}. \qquad (21)$$

If T_0 is quadratic and σ linear, as in equation (20), so that

$$\sigma(\zeta)=-\frac{vr_0}{8\pi D}(\mu_1+2\mu_2\zeta),$$

then integration gives

$$c(r,z)=-\frac{vr_0}{8\pi D}\left\{2\mu_2\left[\sqrt{r^2+(z-l)^2}-\sqrt{r^2+z^2}\right]\right.$$
$$\left.+[2\mu_2 z+1]\,\mu_1\log\frac{\sqrt{r^2+(z-l)^2}+l-z}{\sqrt{r^2+z^2}-z}\right\}. \qquad (22)$$

When one is dealing with an actual capillary, T_0 and σ cannot be linear and constant, respectively, since expression (21) is symmetric about the plane $z = l/z$, while linearity of T_0 implies asymmetry in c_0 and in c', hence in $c(P)$, if permeability, h, is assumed constant. However, in treating the case of many capillaries, oriented at random, we shall assume that for each capillary with a given orientation there is another at the same distance with opposite orientation, and shall use equation (21) to express the effect of one capillary.

Distance in this case will be the distance from the central point of the capillary:

$$R = \sqrt{r^2 + \left(z - \frac{l}{z}\right)^2},$$

or, if

$$z - \frac{l}{z} = Z,\ R = \sqrt{r^2 + Z^2}.$$

We shall set $r = Z$ on the average. Now equation (21) becomes

$$c(R)\Big(= c(r, Z)\Big) = \frac{v r_0^2 (T_1 - T_2)}{4Dl} \times \log \frac{\sqrt{R^2 - \frac{lR}{\sqrt{2}} + \frac{l^2}{4}} - \frac{R}{\sqrt{2}} + \frac{l}{2}}{\sqrt{R^2 + \frac{lR}{\sqrt{2}} + \frac{l^2}{4}} - \frac{R}{\sqrt{2}} - \frac{l}{2}} \tag{23}$$

Since we are interested only in the effects of distant capillaries, we shall assume l is small compared with R and shall hence subtract $\frac{1}{8}l^2$ from the radicands in both numerator and denominator of equation (23), thus making the radicands perfect squares. Now it is easy to integrate $c(R)$ over the volume between $R = R_1$ and $R = R_2$. This integration will give us an expression for contributions to concentration at point P of all capillaries lying between two spherical surfaces of radii R_1 and R_2, respectively, with their centers at P. $R_2 > R_1$. What we are doing here is treating these capillaries as a producing/consuming continuum rather than as discrete producing/consuming bodies; we shall obtain $\sum c_i(P)$ [see equation (17)] for the case in which all capillaries within a sphere of radius R_1 have ceased to flow. if the tissue has radius R_2.

$$\sum_i c_i(P) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl} \left\{ R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} \right. \tag{24}$$
$$\left. + \frac{l^3}{8} \log \frac{R_2^2 - \frac{l^2}{4}}{R_1^2 - \frac{l^2}{4}} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} + \frac{1}{2}l(R_2^2 - R_1^2) \right\} .$$

Here n is the number of capillaries per cubic centimeter between R_1 and R_2. $A(P)$ will be given by the following integration:

$$A(P) = \frac{Q}{4\pi D} \int_0^{R_2} \frac{4\pi R^2}{R} \, dR = \frac{Q}{2D} R_2^2 . \tag{25}$$

Thus, by combining equations (24) and (25) in accordance with equation (17), we obtain

$$c(P) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl} \left[R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} \right. \tag{26}$$
$$\left. + \frac{l^3}{8} \log \frac{R_2^2 - \frac{l^2}{4}}{R_1^2 - \frac{l^2}{4}} + \frac{1}{2}l(R_2^2 - R_1^2) \right] + \frac{Q}{2D} R_2^2 .$$

Equation (26), then, enabling us, as it does, to calculate concentration in a region whose capillaries are not flowing, should be susceptible to experimental verification.

An assumption which must be made concerning tissue is that, if equivalent capillaries are uniformly distributed, n per unit volume, throughout tissue, each capillary produces/consumes exactly one n-th as much of any metabolite as is consumed/produced in a unit volume of tissue. This must be true if the tissue is in a steady state.

If, as in the case we are considering, the capillaries inside a sphere of radius R_1 are not flowing, then capillaries at distances from the center not much greater than R_1 will have to supply/consume some of the material that normally would have been supplied/consumed by the capillaries inside the sphere. For this reason they will have values of σ greater in absolute magnitude than the average value for the whole tissue; hence equation (26) is not accurate, since σ in fact should be a function of R and so should have been included in the integrand. This correction we shall neglect.

Whatever may be the correction to σ for the closer capillaries, it will be seen that the more distant capillaries will be less affected by the absence of capillaries within the sphere of radius R_1; as R approaches infinity, the correction approaches zero, so that capillaries at infinite distance from P will each produce/consume exactly as much material as is consumed/produced in one n-th unit volume of tissue at infinite distance. Hence,

$$\lim_{R_2 \to \infty} \frac{dc(P)}{dR_2} = 0. \tag{27}$$

Application of equation (27) to equation (26) will give us a relation between Q and $(T_1 - T_2)$ in terms of the other quantities involved:

$$\lim_{R_2 \to \infty} \frac{\pi n v r_0^2 (T_1 - T_2)}{Dl} \left[R_2 \log \frac{R_2 + \frac{l}{2}}{R_2 - \frac{l}{2}} \right] + \frac{Q}{D} = 0, \tag{28}$$

whence

$$\frac{\pi n v r_0^2 (T_1 - T_2)}{D} R_2 + \frac{Q}{D} R_2 = 0$$

or

$$\pi v r_0^2 (T_1 - T_2) = -\frac{Q}{n}. \tag{29}$$

Equation (29) is identical with the relation between Q and $(T_1 - T_2)$ obtained by a different method.

If blood is flowing with velocity v in a capillary of radius r_0, then the volume of blood passing a given point per unit time is $\pi r_0^2 v$. Then, if the concentration of some substance is T_1 at the entering end of the capillary and T_2 at the other end, the blood entering per unit time contains a mass of the substance equal to $T_1 \pi r_0^2 v$, while the mass contained in the blood leaving per unit time is $T_2 \pi r_0^2 v$. Hence, in unit time, the blood loses $(T_1 - T_2) \pi r_0^2 v$, or gains $(T_2 - T_1) \pi r_0^2 v$, mass units. Now, if there are n capillaries per unit volume of tissue, and if we assume each capillary to produce/consume as much of the substance as is consumed/produced by a volume $1/n$ of tissue, then

$$(T_1 - T_2) \pi r_0^2 v = -\frac{Q}{n} \tag{30}$$

if Q is production per unit volume of tissue. Equation (30) is seen to be identical with equation (29). This fact does not constitute a verification of our assumption that σ is constant, since the assumptions leading to equations (29) and (30) are equivalent for any $\sigma(\zeta)$, and thus must lead to the same equation. Hence the identity of (29) and (30) merely indicates that the error introduced in the approximation used in integrating equation (23) vanishes as R approaches infinity.

If we now substitute for Q in equation (26) its value as given by equation (29), we obtain

$$c(P) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl} \left[R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{1}{4}l^2}{R_1^2 - \frac{1}{4}l^2} - \frac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 \right]. \tag{31}$$

It is now possible to obtain an expression for concentration at any point $\mathcal{P}$ at distance $\mathcal{R}$ from point P, if $\mathcal{R} < R_1$ and if we assume the field within the sphere of radius R_1 about P is spherically symmetrical. This comes from solution of the diffusion equation

$$\nabla^2 c = -\frac{Q}{D}$$

whose solution for this case is

$$c(\mathcal{R}) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl} \left[R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{1}{4}l^2}{R_1^2 - \frac{1}{4}l^2} - \tfrac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 + \tfrac{1}{2} l \mathcal{R}^2 \right]. \tag{32}$$

All the foregoing treatment has been carried through on the assumption that Q is constant. Whether or not this will in general be true is difficult to say; Landahl has, however (Rashevsky, 1940), obtained relations between concentration and consumption for glucose and oxygen, respectively. These relations show that, as concentration of either of these substances outside a cell increases, the cell's consumption of this substance approaches an asymptotic value $-Q^*$. It is possible to define in each case a value c^* of external concentration such that Q may be considered equal to Q^* if and only if $c > c^*$. It seems also reasonable to assume that metabolism of other substances depends upon the metabolism of oxygen and glucose in such a way that if oxygen and glucose concentrations, denoted by C and C' respectively, are greater than their critical values, C^* and C'^*, all productions and consumptions are constant, provided the constants of the cells in the tissue do not change. Hence, our treatment is valid if and only if $C \geqq C^*$ and $C' \geqq C'^*$. In Rashevsky, 1940, we find expressions for C and C':

$$C = \chi \frac{Q}{Q^*} + \frac{\xi Q}{Q^* - Q} \tag{33}$$

$$C' = \chi \frac{Q'}{Q'^*} + \frac{\xi' Q'}{Q'^* - Q'} . \tag{34}$$

Here Q, Q^*; Q', Q'^* are consumption and critical consumption of oxygen and glucose, respectively. ξ, ξ', χ, χ' are constants given in Rashevsky, 1940; my χ is Rashevsky's ζ. These constants depend, in particular, upon the nature of the cells in the tissue.

Now we set

$$\begin{aligned} C^* &= \chi + \xi \\ C'^* &= \chi' + \xi'. \end{aligned} \tag{35}$$

These are the values of C and C' at which the straight lines tangent to the $C(Q)$ and $C'(Q')$ curves, respectively, at the origin, intersect the lines $Q = Q^*$ and $Q' = Q'^*$. They seem reasonable values for C^* and C'^*.

If we now substitute for T_1, T_2, D the values $\mathcal{T}_1$, $\mathcal{T}_2$, $\mathcal{D}$; $\mathcal{T}_1'$, $\mathcal{T}_2'$, $\mathcal{D}'$ for the special cases of oxygen and glucose, respectively, and substitute for $c(P)$ in equation (31) the values of C^* and C'^* from equation (35), we obtain

$$\begin{aligned} \chi + \xi = {} & \frac{\pi n v r_0^2 (\mathcal{T}_1 - \mathcal{T}_2)}{3\mathcal{D} l} \Bigg[R_2^3 \log \frac{R_2 + \frac{1}{2} l}{R_2 - \frac{1}{2} l} \\ & - R_1^3 \log \frac{R_1 + \frac{1}{2} l}{R_1 - \frac{1}{2} l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{1}{4} l^2}{R_1^2 - \frac{1}{4} l^2} - \tfrac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 \Bigg] . \\ \chi' + \xi' = {} & \frac{\pi n v r_0^2 (\mathcal{T}_1' - \mathcal{T}_2')}{3\mathcal{D}' l} \Bigg[R_2^3 \log \frac{R_2 + \frac{1}{2} l}{R_2 - \frac{1}{2} l} \\ & - R_1^3 \log \frac{R_1 + \frac{1}{2} l}{R_1 - \frac{1}{2} l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{1}{4} l^2}{R_1^2 - \frac{1}{4} l^2} - \tfrac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 \Bigg] . \end{aligned} \tag{36}$$

These equations give the conditions that concentrations of oxygen and glucose, respectively, are as low as they can be if metabolism is to remain constant as concentration changes. If R_1^* and $R_1'^*$ are the values of R_1 for which these two equations are true, then the smaller of these is the radius of the largest sphere of capillaries whose ceasing to flow will not decrease metabolic rate at any point of the tissue.

If we divide each equation (36) by the (positive) coefficient in front of the brackets on the right side, we get two equations, in each of which the quantity on the right side is the same decreasing function of R_1. Hence, $R_1^* < R_1'^*$ if

$$\frac{3\mathcal{D}l(\chi+\xi)}{\pi n v r_0^2(\mathcal{T}_1-\mathcal{T}_2)} > \frac{3\mathcal{D}'l(\chi'+\xi')}{\pi n v r_0^2(\mathcal{T}_1'-\mathcal{T}_2')} \tag{37}$$

or if

$$\frac{\mathcal{D}(\chi+\xi)}{\mathcal{T}_1-\mathcal{T}_2} > \frac{\mathcal{D}'(\chi'+\xi')}{\mathcal{T}_1'-\mathcal{T}_2'}.$$

Thus we see that if the inequality (37) is true, oxygen is the critical substance in maintenance of asymptotic metabolism; otherwise, glucose is the critical substance.

Once we have discovered whether or not inequality (37) is true, we know which of the equations (36) to solve for R_1. It is to be expected that when R_1 exceeds this value, the metabolism of the cells in the center of the sphere of non-flowing capillaries will considerably slow down, and in some tissues, notably in brain and in striated muscle, the cells may begin to die.

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THEORY OF CELLULAR PULSATIONS

HENRY E. STANTON
THE UNIVERSITY OF CHICAGO

The frequency of periodic elongations of a cell has been calculated as a function of the cell volume for Rashevsky's dynamical theory of a cell.

In the interest of more adequate experimental verifications of the existing theory of cellular pulsations, it becomes desirable to make some sort of calculations of the frequencies, as given by the theory. While any exact or absolute value of the frequency cannot be made because of the present lack of experimental data, it is possible to determine how the frequency should vary with the various factors involved. The following calculation consists of a discussion of the expected variation of frequency as a function of the total volume of the cell, since it seems likely that variations of the volume may be performed most simply in an experiment.

One might expect these calculations to be applicable to certain experiments, one of which might be amoeboid movements. An amoeba is, of course, highly irregular, but by measuring its area in a photograph, and dividing by its perimeter, some quantity which might be considered a rough approximation of its elongation would be obtained. This function might fluctuate very sporadically with time, but some approximate value of the average frequency would be found. The amoeba's volume could then be changed by micro-dissection and thus, the curve of the variations of frequency with volume measured.

N. Rashevsky (1939) has developed a theory of cellular dynamics where he finds

$$\begin{aligned} \frac{d}{dt}(a-a_2) &= A_1(a-a_2)+B_1(c-c_2) \\ \frac{d}{dt}(c-c_2) &= A_2(a-a_2)+B_2(c-c_2) \end{aligned} \tag{1}$$

where a is one half the length of an approximately cylindrical cell, c is a linear function of the average cell concentration, and

$$A_1 = \left(\frac{5V}{2V_c} - 1\right)\frac{\gamma a_2^{1/2}}{2\eta a_0^{3/4}}; \qquad A_2 = -\frac{q}{a_0}\left[\frac{D_e}{\left(\frac{3V}{V_c} - 2\right)D_i}\right]^{2/3}$$

$$B_1 = -\frac{R\mu T a_0\left(\frac{3V}{V_c} - 2\right)^{5/3}}{6M\eta}\left(\frac{D_i}{D_e}\right)^{2/3};$$

$$B_2 = -\frac{3}{a_0^2}\left[D_e D_i^2\left(\frac{3V}{V_c} - 2\right)^2\right]^{1/3}; \qquad V_c = \frac{12\pi M D_i \gamma}{R\mu q T} \tag{2}$$

$$a_0 = \left(\frac{3V}{4\pi}\right)^{1/3}; \qquad a_2 = a_0\left[\left(\frac{3V}{V_c} - 2\right)\frac{D_i}{D_e}\right]^{2/3};$$

with V the volume of the cell, and the remaining notation the same as that used by N. Rashevsky. It was shown by him that undamped periodic elongations occur if

$$A_1 + B_2 = 0; \qquad A_1 B_2 - B_1 A_2 > 0\,. \tag{3}$$

Damped periodic elongations will occur if the first of these relations fails, provided that the frequency ω, given by

$$\omega^2 = A_1 B_2 - B_1 A_2 - \tfrac{1}{4}(A_1 + B_2)^2, \tag{4}$$

does not have imaginary values. The vanishing of this expression, then, gives limits to the values of the parameters for which the cell may oscillate. It is the purpose of this paper to find the frequency as a function of the volume V of the cell.

Set

$$y = -\frac{3V - 2V_c}{V}; \qquad u = \frac{\gamma}{2\eta}\left(\frac{V_c}{36\pi D_e^2 D_i}\right)^{1/3}; \qquad v = \frac{\eta V_c}{2\pi\gamma D_i}. \tag{5}$$

Substitution of equations (2) and (5) into (4) gives

$$v\omega^2 = y\left[\frac{2}{3+y} - \frac{u}{4y^{1/3}}\left(\frac{2-y}{3+y} + \frac{y^{1/3}}{u}\right)^2\right]. \tag{6}$$

N. Rashevsky has shown that a necessary condition for undamped periodicity is that

$$\frac{3V - 2V_c}{V_c} < 0; \qquad V_c > 0 \tag{7}$$

and since the cell must produce (i.e. $q > 0$) to be able to oscillate, necessarily

$$y \geqq 0 \tag{8}$$

irrespective of the values of u or v, both of which are positive.

Also, for real ω,

$$\frac{2}{y+3} - \frac{u}{4y^{1/3}}\left[\frac{2-y}{y+3} + \frac{y^{1/3}}{u}\right]^2 \geqq 0\,. \tag{9}$$

Equation (6) may be considered as defining $v\omega^2$ as a function of two variables, u and y. The equality sign will give the boundary of the region of the uy-plane where equation (6) has positive values. Simplifications in this operation gives a quadratic in u,

$$\left(\frac{2-y}{y+3}\right)^2 \frac{u^2}{4y^{2/3}} - \left(\frac{y+2}{y+3}\right)\frac{u}{2y^{1/3}} + \frac{1}{4} = 0, \tag{10}$$

which has the solutions

$$u_1 = y^{1/3}\frac{y+3}{(\sqrt{y}+\sqrt{2})^2} \tag{11}$$

$$u'_1 = y^{1/3}\frac{y+3}{(\sqrt{y}-\sqrt{2})^2}. \tag{12}$$

It is clear that $u'_1 > u_1$ for any $y > 0$ and consequently frequencies are obtainable over a region of the uy plane. It can be shown analytically that u_1 is a monotonic increasing function of y which starts at the origin with a vertical tangent and for large values approaches the curve $u = y^{1/3}$ from below. The u'_1 curve rises from the origin (also with a vertical tangent) monotonically to infinity at $y = 2$, returns from infinity for $y > 2$ to some minimum value ($u'_1 = 6.2$) for $y = 44.2$, and then rises again approaching the curve $u = y^{1/3}$ from above for large values of y. For greater clarity, curves are presented in place of the detailed analysis.

A simple numerical substitution will show that equation (6) has possible solutions for any given value of y provided

$$u_1 < u < u'_1\,. \tag{13}$$

This in turn implies that there exist solutions for $0 < u < \infty$ with proper selection of y and conversely. As an example of this, the value $y = 2$ may be selected. Substitution in equation (6) gives

$$v\omega^2 = \frac{4}{5} - \frac{1}{\sqrt[3]{4}\,u} \tag{14}$$

which is a monotonically increasing function of u for $u > 0$. For real solutions of ω, u must be greater than $\frac{4}{5}\sqrt[3]{4}$ but for large values; $v\omega^2$ approaches the value $\frac{4}{5}$ asymptotically.

If one assumes a certain constant value for y while u varies, then $v\omega^2$ will be a function of u. The salient features of this relationship can be understood by considering vertical sections of the surface representing equation (6). The maxima of this family of curves of intersection will be obtained by equating the partial derivative to zero. Hence from equation (6)

$$\frac{\partial (v\omega^2)}{\partial u} = \frac{y^{2/3}}{4}\left[\frac{2-y}{y+3} + \frac{y^{1/3}}{u}\right]\left[\frac{y^{1/3}}{u} - \frac{2-y}{y+3}\right] = 0. \tag{15}$$

Similarly by considering u as constant,

$$\frac{\partial (v\omega^2)}{\partial y} = \frac{2}{y+3} - \frac{2y}{(y+3)^2} - \frac{u}{4y^{1/3}}\left[\frac{2-y}{y+3} + \frac{y^{1/3}}{u}\right] \times \left\{\frac{2}{3}\left[\frac{2-y}{y+3} + \frac{y^{1/3}}{u}\right] - 2y\left[\frac{5}{(y+3)^2} - \frac{1}{3uy^{2/3}}\right]\right\} = 0. \tag{16}$$

The first of these gives the locus of the extrema of the u-sections and has solutions

$$u_2 = y^{1/3}\frac{y+3}{2-y}; \qquad u'_2 = y^{1/3}\frac{y+3}{y-2}, \tag{17}$$

when $0 \leqq y < 2$ and $y > 2$, respectively, u being always positive. u_2 is a monotone increasing function, and u'_2 decreases from infinity for $y = 2$ to a minimum and finally approaches the function $y^{1/3}$ for large values of y.

The locus of the extrema for the y-sections, which is of primary interest in this paper, follows from equation (16). Simplifying,

$$\frac{(y-2)(6-16y-y^2)}{(y+3)^3}\left(\frac{u}{y^{1/3}}\right)^2 + 3\frac{y^2+6y+6}{(y+3)^2}\left(\frac{u}{y^{1/3}}\right) - 2 = 0. \tag{18}$$

The curves represented by this expression are very complicated to discuss analytically and the results are shown graphically. There are in all six distinct parts to the set, two of which represent minima. The solutions may be found to be

$$u_3 = \frac{3}{2} y^{1/3}(y+3) \times \frac{y^2+6y+6-\sqrt{(y^2+6y+6)^2-\frac{8}{9}(y-2)(y+3)(y^2+16y-6)}}{(y-2)(y^2+16y-6)} \tag{19}$$

$$u'_3 = \frac{3}{2} y^{1/3}(y+3) \times \frac{y^2+6y+6+\sqrt{(y^2+6y+6)^2-\frac{8}{9}(y-2)(y+3)(y^2+16y-6)}}{(y-2)(y^2+16y-6)}. \tag{20}$$

The upper expression is positive for all values of y and monotone increasing. For large y, it approaches the value $y^{1/3}$. The second equation gives positive u'_3 for $0 \leqq y \leqq 0.367$ and $2 < y < \infty$ but for large y approaches the value $2y^{1/3}$. The first set is outside of the region of definition of equation (6) and denotes a minimum. This is true also for the second set for large values of y, but between the value 2 and the minimum point, it represents a true maximum. These results are all shown in Figure 1 which is self-explanatory.

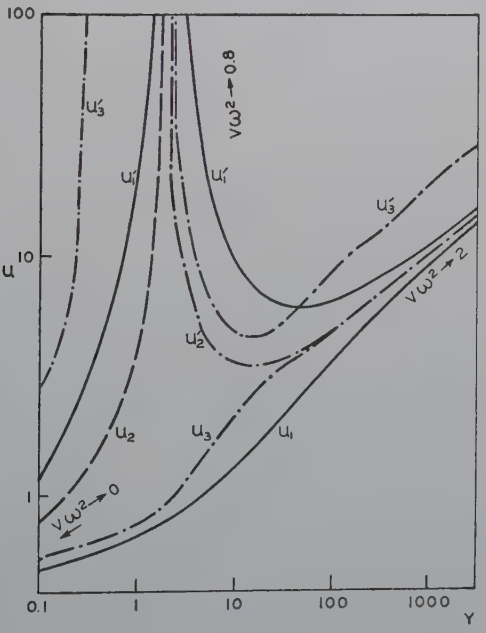

FIGURE 1

In order to study the volumetric dependence of the frequency of an oscillating cell, the analysis given above can be conveniently used to eliminate some calculations. In fact, for a given value of u (to be considered as a parameter) the expected variation of $v\omega^2$ as a function of y may be sketched approximately, knowing the location of the zero points and the maximum. A single calculation of the actual value at the maximum will then give a clear idea of the expected relations which may be compared with experiments. These are shown in Figure 2.

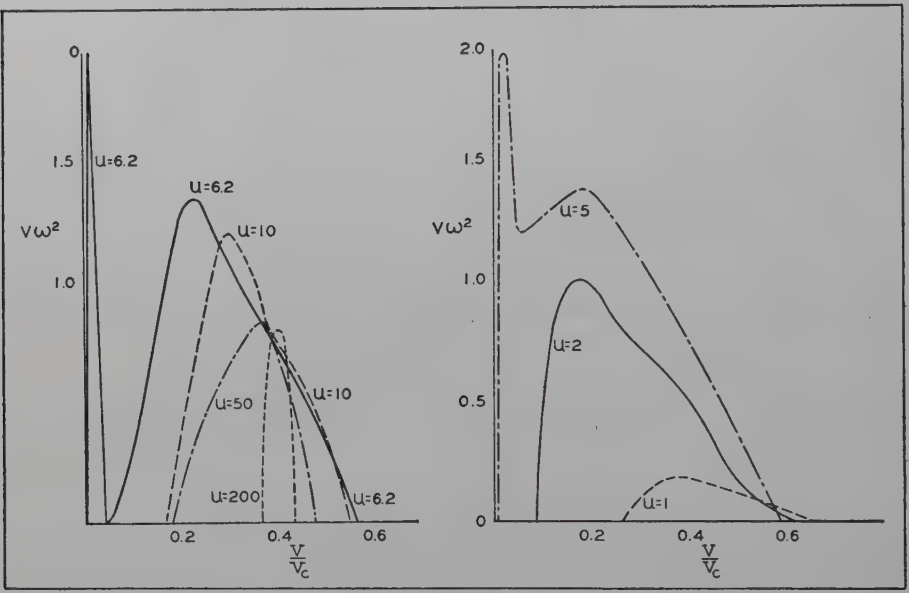

FIGURE 2

Preliminary computations of the parameter u indicate that it has a very high value $\sim$ 500, but the experimental data are very meagre and inaccurate, and much smaller values cannot be excluded from considerations. It is apparent that for $u > 6.3$ approximately, there are two separate regions for y in which oscillations are possible. From equation (5) large values of y imply small values of V, the cell volume, provided V_c remains constant. This would indicate that an oscillating cell would, as its volume is decreased, reach a quiescent state and then begin to oscillate again. It is entirely possible that this is a mathematical property of the equations without biological significance, but there seems to be nothing in the theory to preclude its possibility, except the small size.

If we insert $u = y^{1/3}$, the equation of the maximum for large y, into equation (6),

$$v\omega^2 = \frac{y}{4}\left[\frac{8y-1}{(y+3)^2}\right], \qquad (y \to \infty) \qquad (21)$$

which has the limiting value $v\omega^2 = 2$.

Along the curves $u = y^{1/3}$ and $y = 2$, for very large u, both equations (17) and (19) approach each other. Consequently in the region of definition, both partial derivatives vanish and we would expect absolute maxima for $v\omega^2$. These values are given in equations (14) and (21) and it is consequently apparent that if v is a constant, there is a maximum attainable frequency of oscillation.

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THE LINEAR THEORY OF NEURON NETWORKS: THE DYNAMIC PROBLEM

WALTER PITTS
THE UNIVERSITY OF CHICAGO

The development of a general theory of neuron-networks is here extended to cases of non-steady state activity. Conditions for stability and neutrality of an equilibrium point are set up, and the possible functions representing the variation of excitation over time are enumerated. The inverse network problem is considered—which is, given a preassigned pattern of activity over time, to construct when possible a neuron-network having this pattern. Finally, a canonical form for neuron networks is derived, in the sense of a network of a certain special topological structure which is equivalent in activity characteristics to any given network.

In essaying a treatment of the dynamical case, we shall find it coactive to take into account the finitude of conduction time. We may characterize each fiber of $\mathcal{N}$ by a *total conduction time* θ, defined as the sum of its proper conduction time and the average synaptic delay at the prevening synapse; it is clear that without loss of generality these quantities may be supposed equal. For at least one cannot redargue that their ratios are rational; and this being the case, they have, when expressed in terms of the smallest θ, a least common denominator v. Replace, then, every fiber of total conduction time θ by a chain of $v\theta$ fictitious fibers and synapses, each of which has a total conduction time $1/v$ and suitable thresholds, etc., so as to be otherwise the same as the replaced fiber. If this has been done, we shall measure time in units of $1/v$ in length, so that all total conduction times become unity.

After these preparations we may write a set of equations for the y_i consimilar to the set (2). The principal difference will be this: that if we view the quantities y_i as functions of time, the excitation received by a given synapse s_j from a chain c_k in complete activity will no longer be determined by the *contemporary* value of the excitation at the afferent end of the chain, but rather by its value there for a time-point precedent by an amount equal to the total conduction time of the chain. In our units this latter is ν_i. We may therefore, write

$$y_i = \sigma_i + \sum_j \phi_{ji} \Big\{ \mu_j + \sum_k \psi_{jk}\, \alpha_j\, \beta_j A_j\, y_k(t - \nu_j) + A_j[\Lambda_j(1-\alpha_j) + \Upsilon_j(1-\beta_j)] \Big\} . \tag{1}$$

If we use Boole's operator E, defined by $Ef(x) = f(x+1)$ and having the obvious property $E^m f(x) = f(x+m)$, and change the origin for t by setting $t = t' + \varepsilon$, where ε is the largest of the ν_i, we may write this in the form

$$E^{\varepsilon} y_i = \sigma_i + \sum_j \phi_{ji} \Big\{ \mu_j + \sum_k \psi_{jk}\, A_j\, \alpha_j\, \beta_j\, E^{\rho_j} y_k + A_j[\Lambda_j(1-\alpha_j) + \Upsilon_j(1-\beta_j)] \Big\} , \tag{2}$$

wherein we have set $\rho_j = \varepsilon - \nu_j$ and dropped the prime on t.

If we define the matrix

$$H(E) = \Big|\Big| \sum_j \phi_{ji}\, \psi_{jk}\, A_j\, \alpha_j\, \beta_j\, E^{\rho_j} \Big|\Big| ,$$

this becomes

$$[E^{\varepsilon} I - H(E)]\, y = R , \tag{3}$$

where R is defined as before. It will be noted that when we give to E the value unity, the matrix $H(E)$ reduces to M: this is consonant with the definition of the steady state as a condition where there is no change with time, which is to say,

$$y_i(t+1) = E y_i(t) = y_i(t) = 1\, y_i(t) .$$

If the matrix $E^{\varepsilon} I - H$ be regarded as a polynomial matrix in the indeterminates E, α_i, β_i, we may, by the use of Smiths' process, find unimodular matrices P and Q such that

$$P[E^{\varepsilon} I - H]\, Q = T ,$$

say, is a diagonal matrix whose non-vanishing elements are the invariant factors of $E^{\varepsilon} I - H$; let us denote these factors by

$$T_i[E, \alpha, \beta] ,$$

where i varies from unity to the rank of $E^{\varepsilon} I - H$ and T_i divides T_{i+1}, as is well-known. If we make the substitutions

$$z = Q^{-1} y , \; S = PR ,$$

equation (3) may be written

$$Tz = S , \tag{4}$$

which, in scalar form, is

$$T_i[E\,,\alpha\,,\beta]\,z_i = S_i \qquad [i=1\,,\cdots,P]\,. \tag{5}$$

The system (5) is a set of independent difference equations in the z_i whose coefficients are constants or multilinear in the multipliers. For any region Γ_ρ, these quantities will have determinate values, $\pi_{\rho 1}$, $\pi_{\rho 2}$, and the equations (5) may consequently be solved by the standard methods, the solution holding throughout Γ_ρ. It may be obtained explicitly as follows.

We first derive the solution of the corresponding homogeneous equation, found upon replacing the right-hand side of equation (5) by zero. If we equate the function $T_i[E\,,\alpha\,,\beta]$ to be zero and solve for E as a numerical magnitude, we shall obtain a system of roots, λ_{i1}, λ_{i2}, $\cdots$, λ_{is}, respectively of multiplicity η_1, η_2, $\cdots$, η_s, say. Then the solution in question is given by

$$z_i = \sum_{j=1}^{s} \sum_{k=0}^{\eta_s} a_{ijk}\, t^k \lambda^t{}_{ij}\,, \tag{6}$$

and the quantities a_{ijk} are either constants or, more generally, arbitrary periodic functions of period unity.

To derive a particular solution for equation (5) we must distinguish two cases. In the first, none of the roots λ_{ij} is unity: we find easily by substitution that in this case a constant value for z_i satisfies equation (5); this constant value is $S_i/T[1\,;\alpha\,,\beta]$. In the contrary case there is somewhat greater difficulty. If unity be a root of $T_i[E\,,\alpha\,,\beta]$, of multiplicity r_i, say, we may then put

$$T_i[E\,,\alpha\,,\beta]\,z_i = (E-1)^{r_i}\,\Psi(E) z_i = \Delta^{r_i}\,\Psi(E) z_i = S_i\,, \tag{7}$$

where Δ is the difference-operator; if we make the substitution

$$v_i = \Delta^{r_i} z_i\,,$$

this becomes

$$\Psi(E)\,v_i = S_i\,, \tag{8}$$

in which substitution of a constant value for v_i is permissible, and, as before, yields $v_i = S_i/\Psi(1)$ as a particular solution. To find z_i, we now have the equation

$$\Delta^{r_i} z_i = S_i/\Psi(1)\,,$$

which can be solved immediately as

$$z_i = \frac{S_i}{\Psi(1)}\,\frac{\Gamma(t+1)}{\Gamma(t+1-r_i)\,\Gamma(r_i+1)}\,. \tag{9}$$

This may be added to the solution of the homogeneous equation to yield the general solution of equation (5), which is accordingly

$$z_i = \frac{S_i}{\Psi(1)} \frac{\Gamma(t+1)}{\Gamma(t+1-r_i)\Gamma(r_i+1)} + \sum_{j=1}^{s} \sum_{k=0}^{\eta_s-1} a_{ijk}\, t^k \lambda^t{}_{ij}. \qquad (10)$$

The parameters a_{ijk} are to be determined from the particular circumstances attending the entry of the network $\mathscr{N}$ into the region in question.

It will be instructive to compare the asymptotic behavior of the solution (6) with the results of the purely static analysis made above. We note first in this connection that the presence of unity as a simple or multiple root of some T_i is equivalent to the vanishing of the determinant $|I - M|$: this follows at once from the fact that $E^{\varepsilon} I - H(E)$ becomes $I - M$ when we set $E = 1$, that $T_i[1, \alpha, \beta]$ are consequently the invariant factors of $I - M$, and that the number of vanishing invariant factors of a matrix is equal to its nullity, which by hypothesis is at least unity in the present case. Considering first the case where $|I - M| \neq 0$, we see that equation (10) assumes the form

$$z_i = \frac{S_i}{T_i[1, \alpha, \beta]} + \sum_{j=1}^{s} \sum_{k=0}^{\eta_j-1} a_{ijk}\, t^k \lambda^t{}_{ij}. \qquad (11)$$

The λ_{ij}, none being unity, may be divided here into three groups. First, there are those which exceed unity in absolute value: these constitute say the set Θ_1. Second, those such that $|\lambda_{ij}| < 1$; these may be collected into Θ_2. Finally, those which are -1: these comprise Θ_3. Now if Θ_1 and Θ_3 are both null, the transient term on the left of equation (11) tends to zero with t independently of the initial values, so that the set of y_i correlated to

$$z_i = S_i / T_i[1, \alpha, \beta],$$

if still within the region Γ_ρ in question, are the asymptotic values approached by the network whatever its initial circumstances. We may therefore call this equilibrium point a *stable* one. If this set of values is not within the region—which means that the multiplier-distribution corresponding to it does not satisfy the inequalities (8)—the network will always leave Γ_ρ, however it enters. Now, if Θ_3 is null, but Θ_1 is not, then in general the expression on the right of equation (11) will diverge to infinity with increasing t, either steadily or in the form of explosive oscillations, depending upon the sign and magnitude relations of the members of Θ_1. In a certain particular case, however, namely when $\mathscr{N}$ enters Γ_ρ in such a way that all the coefficients of the terms in the $\lambda_{ij} \varepsilon \Theta_1$ are zero, the system will converge, as before, to $S_i/T_i[E, \alpha, \beta]$, if this lie within the region. This equilibrium point is highly special, since any infinitesimal divergence from the proper initial conditions will lead to a non-zero coefficient of some term in a $\lambda_{ij} \varepsilon \Theta_1$ and consequent explosion. We therefore term this equilibrium point an *unstable* one. We remark that the static analysis does not distinguish these essentially different types of equilibria.

An especially interesting case is that in which either Θ_1 is null or all the coefficients of terms in each $\lambda_{ij} \varepsilon \Theta_1$ vanish, so that we do not have explosion, but Θ_3 is non-null, so that some $\lambda_{ij} = -1$. If certain of these are multiple roots, and we find accordingly terms of the form $a_{ijk} t^k(-1)^t$, which diverge to infinity with t, we shall also suppose the coefficients of these zero, so that the z_i all remain finite. In this case we shall have asymptotically an expression for each z_i of the form

$$z_i = S_i/T_i[E, \alpha, \beta] + B(-1)^t,$$

so that there are standing oscillations of constant amplitude in the steady state, whose amplitude is determined by the initial conditions. This will be a stable or an unstable equilibrium accordingly as we have had to assume zero values for the coefficients of particular terms in equation (11) to avoid explosion or not.

We may now return briefly to the case where $|I - M| = 0$, so that unity is a root of some of the T_i. Here we may distinguish two contingencies: first, where the S_i corresponding to every such T_i vanishes, and second, where this is not the case. The second case, as may easily be verified, is equivalent to the inconsistency of the equations (4) as discussed in the static analysis: here we shall have the particular solution (9) for the z_i; and (11) with this addend always diverges to infinity, so that no equilibrium point of any sort can exist in Γ_ρ—which accords with our previous conclusions. In the first of these cases, however, there is no particular solution to be added, and the appropriate discussion is exactly analogous to that for the case of $\lambda_{ij} = -1$; if all coefficients of divergent terms be made zero, we shall obtain, asymptotically, $z_i = B_{1i} + B_{2i}(-1)^t$, where B_{1i} and B_{2i} depend on the initial conditions, except that $B_{2i} = 0$ if Θ_3 is null. We shall thus have, generally, oscillations of constant amplitude about a baseline determined by the initial conditions, which, in the case $B_{2i} = 0$, leads to an arbitrary parameter in the expression for possible equilibrium points y in Γ_ρ; and since the number of T_i with the root unity is equal to the nullity q of $I - M$, we find that there is a q-dimensional locus of such points in Γ_ρ, in consonance with the results of the static considerations. Which of these equilibria is in fact attained is, of course, to be determined from the manner of entry of $\mathcal{N}$ into Γ_ρ.

Let us define a *network-function* (an N-function) in the following way:

(1). $\sum_{j=0}^{n} (p_j\, x^j)\, a^x$ is an N-function, for any functions p_j of period unity which do not vanish identically, and any constant $a \neq 1$.

(2). Any linear combination of functions of the form (1) is an N-function;

(3). $N(x) + \sum_{j=0}^{r} q_j x^j + K \dfrac{\Gamma(x+1)}{\Gamma(x+1-r)\,\Gamma(r+1)}$ is an N-function where $N(x)$ has the form (1) or (2), K is a constant, the q_j are uniperiodic functions which do not vanish identically, and r is zero or a positive integer.

N-functions of the form (1) and (2) will be said to be of *zero-order*; those of the form (3) to be of *order* r. Moreover, we shall consider any two N-functions to be *equivalent* if one arises out of the other by substituting any functions of period unity which do not vanish identically for the p_j and q_j. The excitation in $\mathcal{N}$ within a given region Γ_ρ as a function of time, as given by equation (11), is an N-function and in normal form: we shall call it or any equivalent network function the *characteristic function* of Γ_ρ. Evidently, any characteristic function of Γ_ρ will serve equally well to specify the excitation-function of $\mathcal{N}$ in Γ_ρ.

Given these definitions, we are now in a position to state and prove a theorem which complements the foregoing results by a partial solution of the inverse problem, which is, to determine conditions under which a given set of excitation functions can be realized by a suitable finite nerve-fiber network. We shall have, in fact, the

THEOREM.

Let a given P*-space be partitioned into regions by planes perpendicular to the axes in any desired way, and let a set of* P *functions be specified for each region, one for each coordinate axis: then, that there may exist a finite network* $\mathcal{N}$*, with some pattern of applied external stimulation, and having some set of* P *third-order synapses, such that the course of excitation at each such synapse when the system is in any of the regions* Γ_ρ *is given by the function specified for the corresponding coordinate axis in* Γ_ρ*, it is sufficient that the following conditions be fulfilled:*

(A). *Each of the specified excitation-functions must be an* N*-function.*

(B). *The given partitioning of* P-*space will define a set of multipliers analogous to those we have used above, though not necessarily univocally; and throughout every given region* Γ_ρ *these multipliers will have a single value-distribution* $\pi_{\rho 1}, \pi_{\rho 2}$. *Moreover, for every such distribution* $\pi_{\rho 1}, \pi_{\rho 2}$ *such that no pair* α_j, β_j *are simultaneously zero, there is a corresponding region* Γ_ρ. *Then the condition is that, for some admissible set of multipliers, every region* Γ_ρ *whose specified excitation functions are not all constant must have at least one pair of multipliers* α_i, β_i *simultaneously unity.*

In particular, given these conditions, it is possible to find a set of independent networks each of which consists of n simple circuits with one common synapse (we shall term these networks, which contain just one third-order synapse *rosettes*), such that $\mathcal{N}$ arises by running chains *from* the centers of the rosettes to various designated points outside: but none back, so that the state of the whole network is determined by the states of the separate rosettes independently. We shall call networks of this kind *canonical* networks.

In the proof, it will evidently be enough to construct a separate such $\mathcal{N}$ for each dimension of P-space separately, since the $\mathcal{N}$ of the theorem is then the aggregate of these separate sub-networks.

Now to every network function

$$N_i(x) = \sum_{j=1}^{\nu} \sum_{k=0}^{\mu_{ij}} p_{ikj}\, x^k\, a^x{}_{ij} + \sum_{k=0}^{r} p_k\, x^k + b\, \frac{\Gamma(x+1)}{\Gamma(x+1-r)\, \Gamma(r+1)}$$

in normal form we may correlate a set of polynomials in E

$$\Psi_i{}^n(E) = E^n (E - a_{i1})^{\mu_1} (E - a_{i2})^{\mu_2} \cdots (E - a_{i\nu})^{\mu_\nu},$$

which differ among themselves only in a zero root of varying multiplicity n. Let a suitable such polynomial be chosen, and denote the coefficient of E^m in it by $\theta_m{}^n(N_i)$, where n is the multiplicity of its zero root.

Consider now a given region Γ_i, to which our hypothesis assigns a non-constant network-function N_i, and let it have a set of characteristic multipliers of which one pair, say α_j, β_j, corresponding to the limits Λ_j, Υ_j are both unity. Now construct a rosette $\mathcal{R}$ in the following manner: if $\Psi_i{}^s(E)$ be of the n-th degree in E, $\mathcal{R}$ is to have $n - s$ circuits, $C_n, C_{n-1}, \cdots, C_s$, having respectively $n, n-1, \cdots, s$ fibers apiece. All the circuits are to have the same limits, namely Λ_i and Υ_i— this can evidently be secured in every chain of sufficient length, and here they are all longer than an arbitrary s—and the circuit C_p is to have an activity parameter $A_p = \theta^s{}_{n-p}(N_i)$. We shall suppose that $B_R = \sigma_i + \sum_j \mu_{ij}$, σ_i being the external stimulation at the center of $\mathcal{R}$; but σ_i and the μ_{ij} may be otherwise arbitrary.

Now consider the course of activity in $\mathcal{R}$. By the appropriate case of equation (2) above, we find for this the equation

$$\left[\sum_{\rho=1}^{n} \theta_\rho{}^s(N_i) E^\rho\right] y_i = \Psi(E) y_i = B_R\,, \tag{12}$$

where y_i is the excitation at the center of $\mathcal{R}$. As before, we find the solution of this to be

$$\begin{aligned} y_i = {} & \sum_{j=1}^{v} \sum_{k=0}^{\mu_{ij}} p_{ijk} x^k a_{ij}{}^x + \sum_{k=0}^{r} p_k x^k \\ & + \left\{ B_R \left[\frac{\Psi(E)}{(E-1)^r}\right]_{E=1} \right\} \frac{\Gamma(x+1)}{\Gamma(x+1-r)\,\Gamma(r+1)}\,, \end{aligned} \tag{13}$$

which becomes $N_i(t)$ when we set

$$B_{R_i} = b/[\Psi(E)/(E-1)^r]_{E=1}\,.$$

We shall suppose that rosettes $\mathcal{R}_i$ have been constructed in this manner for every region Γ_i with a pair $\alpha_j = \beta_j = 1$.

Suppose now that π_{i1}, π_{i2} is the multiplier-distribution for Γ_i, and consider the function

$$\Phi_i = \prod_{i,j\varepsilon\pi_{i1}} (1-\alpha_i)(1-\beta_j) \prod_{i,j\varepsilon\pi_{i2}} \alpha_i \beta_j\,. \tag{14}$$

Evidently, for the set of values for the multipliers π_{i1}, π_{i2}, Φ_i is unity, while for any other such distribution, it vanishes. Φ_i may be written out as a polynomial:

$$\Phi_i = \sum_{j,k} W_{j,k}\, \alpha_{j1}\, \alpha_{j2} \cdots \alpha_{jm}\, \beta_{k1}\, \beta_{k2} \cdots \beta_{kn}\,, \tag{15}$$

in which every $W_{jk} = \pm 1$.

The reader will easily see that if any two chains c_p, c_q have limits Λ_p, Υ_p; Λ_q, Υ_q, respectively, and corresponding multipliers α_p, β_p and α_q, β_q, the result of putting them in series has the multipliers $\alpha_p\,\alpha_q$ and $\beta_p\,\beta_q$. It follows that taking each term on the left of equation (12), say $W_{hk}\,\alpha_{h1}\,\alpha_{h2}\cdots\alpha_{hm}\;\beta_{k1}\;\beta_{k2}\cdots\beta_{kn}$, we may construct a chain c_{hk} whose lower multiplier is $\alpha_{h1}\,\alpha_{h2}\cdots\alpha_{hm}\;\beta_{k1}\cdots\beta_{kn}$; and we shall assign to it the activity parameter $A_{hk} = W_{hk}$, and a $\mu_{hk} = 0$.

Now, taking the center of some one $\mathcal{R}_i$ of the constructed rosettes, say a synapse s_i, and an arbitrary external synapse s_k, connect a chain c_{hk} of this kind from s_i to s_k for each term on the right of equation (15). By the definition of Φ_i, the excitation at s_k will then be the same as at s_i when the multipliers have the distribution π_{1i}, π_{2i}; otherwise it will vanish. Now, if we connect every rosette $\mathcal{R}_i$ to s_k in this manner, then whenever we are in some region Γ_i with a multiplier-distribution π_{i1}, π_{i2}, we shall have $y_k = N_i(t)$, which is the N-function required in the hypothesis. If, however, we have $y_k =$ constant in Γ_i, we can have simply a single synapse s_i, with a suitable external stimulation, connected to s_k in the same manner, instead of a rosette; and this will give the proper results at s_k. Since we can make a construction of the above type for every dimension of P-space, the theorem follows. In particular, it will be noted that by this method we may distribute equilibria of various types among the regions subject only to the conditions of the theorem. The necessity of the condition (A) of the theorem will be found evident.

We may conclude by noting an immediate

COROLLARY

Given any finite network $\mathcal{N}$, *it is possible to find a set of independent rosettes such that the excitation function of* $\mathcal{N}$ *for every region is a linear combination of those of the rosettes—i.e., we can reduce any network to a canonical network having the same excitation function.*

In an intended sequel we shall consider the extension of results of the above type to networks governed by the two-factor excitation theories, instead of the present simplified linear model. We shall there develop the subject primarily from the standpoint of the inverse network problem, since it seems probable that it is here that the most fruitful and practically useful results are likely to be obtained.

In conclusion I wish to express my appreciation to Dr. A. S. Householder for his perspicacious counsel and criticisms.

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OUTLINE OF A NEW MATHEMATICAL APPROACH TO GENERAL BIOLOGY: I

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

This first part of the paper deals with the theory of organic form. By introducing a formal principle, it is possible to develop a mathematical theory of shapes of organisms, which covers both animals and plants.

The development of Mathematical Biophysics has made considerable strides in the last years. Not only is the theoretical edifice wall erected and systematically developed, but a very large number of experimental facts ranging from cell respiration to experimental aesthetics have been adequately quantitatively represented and in some cases even predicted by the theory.

Naturally, as in every science, the more a theory is developed the more new problems appear in it. Also the more experimental facts have been explained, the more new experimental facts call for an explanation. The progress of any science may almost be measured by the width of the new horizon it uncovers to us.

Whether there is such a thing as a possible exhaustion of a science, a stage in which everything is discovered and nothing remains to be done, is more a metaphysical question, and we shall not discuss it here. Premature worries in regard to the possibilities of explaining some of the yet unexplained phenomena, and anxieties lest such an explanation should turn out to be impossible, should not take place with scientists. Whenever such worries and anxieties have taken place, they usually were rather ridiculed by further developments by investigators who went ahead heedless of such worries.

Nevertheless, at every stage of development of a science, when we have before us a vista of unsolved problems, it is useful, and perhaps even necessary to consider, so to say, the general plan of campaign in attacking those problems. We may not be expected to tell actually how to solve those problems, for that would practically amount to a solution. But we should be able to see at least in principle how those problems may be solved practically.

If we survey from this point of view the field of mathematical biophysics, we find that while in some directions the method of further conquest is already indicated by merely following and extending present techniques, in some other directions the adoption in the future of new methods and techniques is strongly indicated.

The first case is exemplified mainly by the mathematical biophysics of the central nervous system. We may have to modify somewhat the fundamental equations. But in principle the rather formal method used hitherto, namely the study of geometrically more and more complex circuits, to which the formal, phenomenological equations are applied, still offers almost unlimited possibilities.

The second case is exemplified by the mathematical biophysics of the cell, especially of cell aggregates and of the organism as a whole. While by the introduction of drastic simplifications, a remarkable progress has been made in the dynamics of cell division, as well as in the theory of cell aggregates, yet an impartial survey of the situation shows that it is pretty difficult to even conceive in principle how the present methods are going to be applied *practically* to some more complex cases. We have outlined a couple of possible approaches to the problem of the form of animals. In principle the development of those suggested approaches should well lead us to the solution of the problem. *Practically,* however, as it is easy to see even now, we shall soon run into almost insuperable difficulties if we try to extend even the present approximate treatment of the metabolic forces to such complex shapes as are offered by various organisms. Any oversimplification of the problem must have a limit, beyond which the problem becomes completely distorted and unreal and a further simplification of the present "approximation method" would likely exceed that limit. Something else is to be done.

Difficulties of a similar nature but perhaps even more severe in extent, are met when we remember that hitherto mathematical biophysics has studied only a very, very small section of the organic world. The interaction between the organisms and the surrounding environment has been taken into account from the very beginning. This interaction forms often a very essential feature of the theory, as for instance in the case of cell division. Yet the properties of the environment considered have been oversimplified almost to the limit. Only a very small fraction of the environment of an organism is inorganic. The largest part of that environment is formed by other organisms. Almost every organism depends for its existence on the presence of other organisms, with the exception perhaps of some simplest unicellular organisms. With this exception the concept of an organism or even of a number of organisms of the same kind, in the absence of other kinds of organisms, is a fiction.

Again we may say, or at least we may hope, that in the final analysis all these complex interactions are reducible to physico-chemical metabolic forces of tremendous complexities. But that very complexity makes it again rather doubtful, whether *practically* we may achieve anything by such a reduction. Again something else is to be done.

Situations of that nature are not unfamiliar to the physicist. The latter does not doubt that even the most complex mechanical or electromechanical phenomena are ultimately reducible to activities of individual atoms. Nevertheless in studying for instance a complex electric circuit, a physicist does not fall back on the equations of the electron theory, but uses some general *formal* principles in his computations. It is quite true that at present almost all such formal principles can be shown directly to be deducible from atomic theory. But there was a time when this was not known, and yet those formal principles were used just as safely. We may be reminded by way of example of Fourier's theory of heat conduction, Ohm's law, etc.

We therefore propose to introduce in mathematical biology a few such formal principles, which may be used to advantage in the development of a theory of more complex biological phenomena, regardless *at present* of their reducibility to the principles used hitherto. It must be kept in mind, that the adoption of such formal principles does in no way compete with the use of the former ones, which are more *physical* and less formal in nature. The two sets are quite compatible. The introduction of the formal principles opens however new horizons, hitherto unseen.

It may be worth noticing, that the mathematical biophysics of the central nervous system, which offers, as we remarked, almost unlimited possibilities for further developments with the present method, is essentially based on a few formal phenomenological principles.

I. Organic Form

Whether a single cell or a complex metazoan or plant, every organism is a metabolizing system. But whereas in a single cell metabolism is perhaps the most outstanding thing, complex metazoan organisms are usually characterized by other essential physico-chemical attributes. One of the most important of those, which occur in single cells even, is motility. Another important attribute is the nervous coordination and integration. The velocity of locomotion of any organism varies largely under different circumstances. We may however consider every mobile metazoan as endowed with an *average* velocity of locomotion, v, characteristic of the species. Similarly the amount of nervous coordination and integration varies largely from case to case. But again we may consider average values, characteristic of the species. This average amount of coordination will be some increasing function of the amount n of nerve tissue per unit mass of the organism.

With the exception of some protozoa, the locomotion of all organisms is produced by a system of levers. In such cases as snakes or fishes the body as a whole is used as a lever. In other cases the extremities are such systems of levers.

Although quite a considerable amount of research has been done on the kinematics of movements of the vertebrates and of some other organisms, (Bethe 1930), a systematic theory of what may be called *lever-propelled metabolizing systems* is yet completely lacking. An elaboration of such a systematic abstract theory, as a preliminary to actual biological applications, is strongly indicated.

Given a metabolizing system of mass M, average metabolism q ergs gm^{-1} per unit mass, average amount of nervous tissue nM gm., the average velocity of locomotion v will be determined by the particular structure of the systems of levers which constitute the locomotory system. If we have a systematic classification of such systems of levers and of their properties, we can calculate for a given lever system, the value of v in terms of M, q and n. In general we may expect that for given M, q and n the same value of v may be obtained by means of several lever structures.

In developing a systematic theory of lever propelled metabolizing systems, we shall amongst other things classify those systems by their degree of complexity. Provisionally we may consider the complexity as measured by the number of single rigid levers of the system. A more detailed theory should, however, take into consideration also the different types of joints between the levers. A joint with two degrees of freedom will be considered as more complex than a joint with one degree of freedom. In such a case the complexity may be measured by the number of kinematic degrees of freedom of the whole system.

We shall now introduce the following formal principle.

A lever propelled metabolizing system, characterized by given values of M , q , n *and* v *has the simplest lever structure which for the given values of* M , q *and* n *gives the required value of* v .

Since the lever structure of an organism determines to a large extent its shape, we thus may describe the shape of an organism in terms of M, q, n and v.

Not much can be done with the above principle until the actual theory and systematics of lever propelled systems is sufficiently developed. In order to show however in what direction such studies should take place, we shall give here a few examples, meant *as illustrations only.*

Let us first consider the simplest case when the system is of a cylindroid shape, flexible along the axis and can itself be used as a folding lever system. In this case which in nature is exemplified by snakes, the locomotion proceeds essentially by alternate folding and unfolding. During the folding the "front" end (Figure 1a) remains in fixed contact with the ground, during the unfolding the "rear" end does it. (Figure 1b). In the locomotion of a snake actually this folding is a double folding (Figure 1c), but this does not change things in principle.

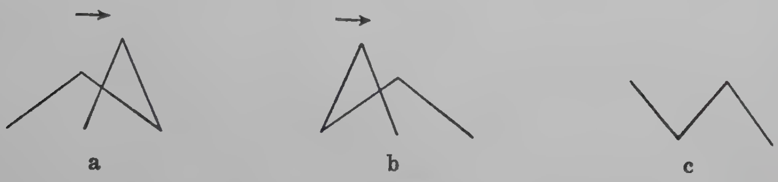

FIGURE 1

This type of movement requires relatively little coordination and therefore a relatively small n will be sufficient. We may set as requirement $n > n_1$, where n_1 is the minimum n required for such types of movements.

For simplicity (since this is an illustration only) let the angle of folding be constant. Then, denoting by ν the frequency of folding and unfolding, by L the total length of the system, and by a a coefficient, we have

$$v = a\nu L \,. \qquad (1)$$

The energy necessary to maintain the system in continuous motion with the average velocity v must be supplied by the total metabolism qM. That energy is essentially composed of two parts. The first part is the overcoming of the frictional resistance of the ground. In dry friction the resistance is independent on the velocity. In that case the work done per unit time is proportional to v. If the resistance is proportional to v, then the work done per unit time to overcome that resistance is proportional to v^2. Moreover, for dry resistance it will be proportional to M, for the friction will increace with M. The second part of the energy is that required to actually produce contractions of the muscles involved, and is per unit time proportional to the mass of the muscles and to ν. Since in the case considered the whole body participates in the locomotion the mass of the muscles may be put equal to M.

Denoting by c and f two more coefficients and considering that practically the whole metabolism contributes to the locomotion, we have for the case of dry resistance

$$qM = cMv + f\nu M\,, \tag{2}$$

or

$$\nu = \frac{q - cv}{f}. \tag{3}$$

Equations (1) and (3) give

$$v = \frac{a(q - cv)L}{f}. \tag{4}$$

The length L for a given shape varies as $M^{1/3}$. Putting for simplicity the average density δ of the system as equal to 1 (which it practically always is) we may write

$$L = \alpha M^{1/3}, \tag{5}$$

α being a form factor. Considering the shape of the organism as a very oblong ellipsoid of revolution with major semiaxis r_1 and minor r_2, and putting

$$\frac{r_1}{r_2} = \lambda \tag{6}$$

we have

$$\frac{4}{3}\pi r_1 r_2^2 = M$$

or because of equation (6)

$$\frac{4}{3}\pi \frac{r_1^3}{\lambda^2} = M. \tag{7}$$

Hence

$$L = 2r_1 = 2\sqrt[3]{\frac{3\lambda^2}{4\pi}}\,M^{1/3}. \tag{8}$$

Equations (5) and (8) give

$$\alpha = \sqrt[3]{\frac{3\lambda^2}{4\pi}} \quad \text{or} \quad \lambda = \sqrt{\frac{\pi\alpha^3}{6}}. \tag{9}$$

From equations (4) and (5) we have:

$$v = \frac{a(q - cv)\,\alpha\, M^{1/3}}{f}, \tag{10}$$

or

$$\alpha = \frac{fv}{aM^{1/3}(q - cv)}. \tag{11}$$

Hence, if for such a system, M, q and v are given with $n > n_1$, then α is completely determined. But α determines λ by means of equation (9) and λ determines L by means of equation (8). Hence the gross form of the organism is determined.

The quantity α, and hence also λ increase with v. For

$$v = \frac{q}{c} \tag{12}$$

α becomes infinite. Hence the value (12) of v is the greatest that can be obtained for any M and q, with the particular form of the organism.

If

$$v > \frac{q}{c} \tag{13}$$

then the organism must represent a different system of levers, and must possess lever attachments in the form of extremities. We shall presently see, that introduction of extremities does actually raise the limit of v over that given by equation (12).

In principle we may consider any number of pairs of extremities. For simplicity consider them all of the same length l. They may work either alternately or synchronously and the locomotion again consists in a folding and unfolding of each pair, the "rear" member of the pair pushing against the ground in the unfolding process, the "front" member during the folding.

Let us first consider the purely theoretical case that the extremities are rigid levers of length l, that is without knee-joints, etc. Then denoting by a_1 a constant, we have, similarly to equation (1):

$$v = a_1 \nu l, \tag{14}$$

regardless of the number of pairs of extremities. Hence, it would at first appear as if our fundamental formal principle would allow only organisms with only one pair of extremities. This however is not so, if we consider the role of the quantity n. Both locomotion and quiet standing are unstable processes for only one pair of extremities. The maintenance of standing posture with only two extremities requires a very complex mechanism of nervous coordination and hence a sufficiently large n. Let us denote by n_2 the smallest value of n which will provide for the necessary coordination. As a measure of n_2 we may perhaps take the total number of muscular movements, which is involved on the average per unit time in order to maintain an erect posture on two extremities.

If $n \geqq n_2$ then the organism may have only two extremities. This does not mean that it necessarily will have. For if inequality (13) is not satisfied, the minimum number may still be zero. But if (13) is satisfied, and $n < n_2$, then the organism must have at least two pairs of extremities of the rigid type assumed above.

A standing posture on four extremities requires much less coordination, although mechanically it is not quite stable, considering that the extremities are not rigidly joined to the body. A certain minimum amount of muscular coordination is still necessary to maintain a standing position. Let to that minimum correspond a value n_4. Then we find four extremities only within the range $n_2 > n > n_4$. For $n_4 > n > n_6$ we find six extremities, etc.

There is another factor which plays a role in the determination of the number of extremities. That is the size of the organism relative to the average "roughness" of the ground on which it is moving around. Even a human uses all four extremities when climbing over a rough mountainous terrain, when the average size of the "bumps" becomes of the same order of magnitude as that of our bodies. For very rough terrain we have to use our fingers, which are additional levers, to take hold of the unevennesses. Hence a system of even four rigid extremities will not be sufficient in such a case, and it is necessary to introduce additional levers either by adding more joints at the ends of the extremities, or by adding more extremities.

From kinematic considerations it may be readily seen, that in the first instance at least two "fingers" have to be added to each extremity, to provide for sufficient hold. Hence, the second case introduces less additional joints. The smaller number of joints the smaller may be n. Hence for small values of n the stabilization will take place by addition of new extremities. And since the relative roughness of the ground in general increases as the size of the organism decreases, we shall find 6 or 8 extremities for small values of both M and n. Such is the case with insects. When M and n are large, only four extremities may be sufficient but they will be provided with "second order" extremities.

Now we may consider the actual expression for v in terms of M and q. In addition to the overcoming of resistance to the motion and to supplying the energy of muscular contraction, the organism moving by means of rigid extremities must spend with every step some energy on lifting itself (Figure 2). This energy is not recovered in the downward motion, or at least not completely recovered, due to friction etc. Per unit time it is equal to

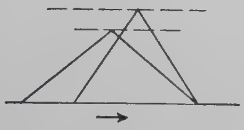

FIGURE 2

$$b \nu l M \tag{15}$$

b being a coefficient.

For the work to overcome the resistance of the ground we shall have the following expression; we may consider that the resistance is exercised everytime the extremity, during the forward motion comes in contact with the ground. That resistance force is roughly proportional to the velocity v, and hence the work of resistance is proportional to v^2. But this work is done only intermittently, the frequency of this intermittent work being ν. Hence the total work is roughly proportional to

$$M \nu v^2 . \tag{16}$$

Denoting by M_e the mass of all the extremities and remembering that now only those are involved in the locomotion, (which is of course only a crude approximation) we have now instead of equation (2):

$$q M_e = b \nu l M + c_1 M \nu v^2 + f_1 \nu M_e , \tag{17}$$

where c_1 and f_1 are different from c and f.

Solving equation (17) for ν and introducing it into equation (14) we find

$$v = \frac{a_1 q M_e l}{bMl + c_1 M v^2 + f_1 M_e} . \tag{18}$$

Introducing a "form factor" β for the extremities, we may put

$$l = \beta M_e^{1/3}, \tag{19}$$

and equation (18) now gives, with $\beta' = l/\beta^3$:

$$v = \frac{a_1 \beta' q l^4}{bMl + c_1 M v^2 + \beta' f_1 l^3} ; \tag{20}$$

which may be written thus:

$$a_1\beta' q l^4 - \beta' f_1 v l^3 - bMvl = c_1 M v^3. \tag{21}$$

Equation (21) determines l for a given set of M, q, ν and β'. It may be shown that equation (21) has always one and only one positive root, l_1, which represents our solution, the negative roots being discarded as physically meaningless. The form-factor β' is determined by mechanical considerations. For a given M_e the length of the extremities is limited by their mechanical strength needed to support the total mass M of the organism. As v increases, l_1 increases. Hence for any M, q and v we may determine a corresponding $l = l_1$. Therefore if inequality (13) is satisfied, crawling is impossible, but running may be possible. The only limitation imposed now is the circumstance, that for a given M, l has an upper limit $l_0(M)$ for purely geometric reasons, since an organism cannot be "all legs". If inequality (13) holds, and if for that v the necessary l is greater than l_0, then neither crawling nor running is possible.

Consider however that each extremity has a "knee joint" and can be folded. In that case the term with b in equation (17) and the following ones may be reduced or eliminated, for there is no need of lifting the organism (Figure 3) as much as before. The result will be a decrease of l for the same values of M, q and v. Now we may have $l_1 < l_0$ for $v > q/c$, and while crawling is impossible, running is possible.

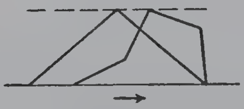

FIGURE 3

If the constants in our equations, which have to be determined by a more exact elaboration of the theory of lever propelled systems, are such, that $l_1 > l_0$ whenever $b > 0$, then for such values of v which satisfy inequality (13) any locomotion will be possible only if the extremities have a knee-joint. That this is so, will be demonstrated in a subsequent paper.

Making more than one knee-joint will not improve anything, and therefore, according to our fundamental principle, such a structure does not occur.

In a similar way we may treat other types of locomotion on the ground. For instance a system based on a structure without extremities may propel itself by successive folding and refolding in the vertical plane, as in the case of some caterpillars. Here the term in v^2 in equation (2) vanishes, but a term similar to that given by (15) appears. A limitation is also imposed by considerations of mass and rigidity. It will be readily found, that for a sufficiently large mass the system will not be rigid enough. The necessary inequalities may be readily derived. But even without deriving them it may be seen that such type of locomotion will occur only in small animals.

All the above is given only as an illustration, pending the necessary development of a systematic theory of lever propelled systems. But our illustration shows, how by combining our fundamental principle with purely mechanical and physical considerations, we may determine the given form of an organism in a unique way for a given set of M, q, and v, n.

Locomotion in water and air is treated essentially in a similar way. Consider for instance locomotion in water by the use of the whole body as a lever (some fishes). We have again, denoting the body length by L and by a_2 a constant

$$v = a_2 \nu L . \tag{22}$$

The resistance now varies approximately as the linear dimensions or $M^{1/3}$. Therefore we have now

$$qM = f_2 \nu M + c_2 M^{1/3} v^2 . \tag{23}$$

This gives

$$v = \frac{qML - c_2 M^{1/3} L v^2}{f_2 M} a_2 \tag{24}$$

and equation (24) determines L in terms of M, q and v.

The treatment of flying is somewhat more complicated, requiring aerodynamical considerations. But in principle it proceeds in a similar way.

It may be readily seen that less energy is required to keep a small organism afloat in the air than a big one. If an organism is falling through air, the air resistance for not too large velocities is approximately proportional to rv, where r is the average linear dimension. (Stoke's law). The force F of weight, pulling it down varies as r^3. Hence $v \propto r^2$. The work done per second by the force of gravity is proportional to $Fv \propto r^5$, while the total metabolic energy available is proportional to $r^3 q$. Hence, from $r^5 \cong r^3 q$ we find that

$$q \propto r^2 . \tag{25}$$

It may be therefore expected that the aerodynamic efficiency of any mechanism used for flying, may be much smaller for small organisms, than for large ones. Hence also the degree of nervous coordination and therefore n, will be much larger for larger organisms.

We may next consider organisms, that can propel themselves in two or three different media, e.g. ground, water and air, with corresponding average velocities v_g, v_w, v_a and determine in the above manner the sizes and number of their legs and wings. As we have seen for $n > n_2$, only two legs will be found. With a large M, as we just have seen, a large n is required for flying. If that value of $n = n_f$ is always larger than n_2, then all large flying animals will have only one pair of extremities for running (birds). For small M, flying does not require such a large n, and the number of extremities for ground locomotion will be larger, as determined by previous considerations.

Thus far we have considered only animals. With some exceptions, plants may be considered as organisms with $v = n = 0$. The problem of form may however be treated also in this case on the basis of similar principles.

First of all, the absence of locomotion and therefore the impossibility of running after the food, will require a much larger specific surface of the organism through which food can be absorbed from the surrounding medium. Hence the general "branched" character of plants. As a further illustration, we shall outline a possible approach to the form of plants.

Let l_0 be the length of the main trunk, r_0 its radius. Let l and r be the average length and radii of the branches. Let the total number of branches be n, and the average density of the plant δ. Then

$$M = \delta (l_0 r_0^2 + n l r^2). \tag{26}$$

Since qM is proportional to the total number of leaves, it is therefore approximately proportional to the area of the branches. Hence

$$qM = knlr, \tag{27}$$

k being a coefficient.

From mechanical considerations, the length of a branch cannot exceed a certain value, determined by its radius, lest the branch break

$$l = f(r, \delta). \tag{28}$$

Since the smaller r, and the greater l, the greater for a given M the specific surface of the tree, if the latter has a maximum, the relation (28) must hold.

Similarly

$$l_0 = f_0(r_0, \delta, M). \tag{29}$$

Moreover, the total flow of metabolites through the trunk is limited by r_0, and the diffusion properties of the material. Considering that r_0 is always just such as to allow the necessary flow, we have for the trunk

$$r_0 = f_1(qM, \delta), \tag{30}$$

and for each branch

$$r = f_1\left(\frac{qM}{n}; \delta\right), \tag{31}$$

Altogether we have six equations, to determine the six quantities l_0, r_0, n, l, r and δ in terms of M and q. But the first five quantities already largely determine the gross shape of the plant. Small l_0 and r_0 and large n, give us a bush. Small l_0, large r_0, small n and large l give us the form of Figure 4a. Large l_0, r_0, n, l and r, give the shape of Figure 4b, while the large l_0, r_0 and n, but small l and r give something like Figure 4c. By using plausible expressions for $f(r, \delta)$, f_0 and f_1 those different forms are actually obtained as functions of M and q. This will be discussed in detail in a subsequent paper.

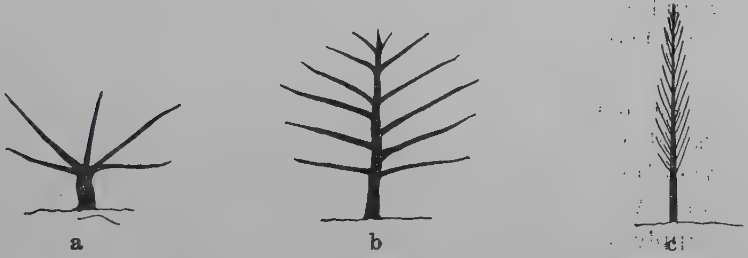

FIGURE 4

Instead of equal branches we may introduce a distribution function $n(l)$, such that $\int_0^\infty n(l)\,dl = n$, and determine $n(l)$ from some extremum requirement.

The shapes of leaves may possibly be related to their mass and metabolic rate. Thus consider a leaf as shown on Figure 5a. Let its mass and hence its size, increase. The distance between the veins becomes greater, until it eventually becomes too great for the metabolites to reach the remotest points. Hence 5a becomes impossible, while shape 5b will be found. The same effect is obtained by increasing q for a constant mass.

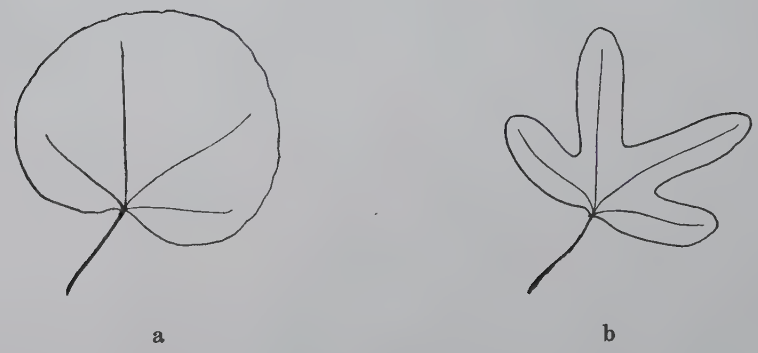

FIGURE 5

Different shades of green of a leaf are determined by the chlorophyll content, and are therefore also linked to q. Combining all these considerations together, we see a way of establishing a relation between M and q, the general shape of a plant, and the size, shape and shade of its leaves, and through δ, the mechanical properties of the wood.

The gist of the whole consideration is that we express the essentially discontinuous properties of the organic form (no extremities, two extremities, six extremities) by a set of continuously varying parameters. We do not need to limit ourselves to M, q, v and n, and we may apply the same procedure to cases, when there are a larger number of determining parameters. Thus in addition to the average velocity of locomotion v we may consider the *maximum acceleration* v of which an animal is capable and which play an important role in its life. This may lead to a theory of jumping, involving considerations of unequal hind and front extremities.

The structure of different sense organs, with which an organism is endowed, may also be treated in a similar way. We shall consider as continuously varying determining parameters such things as acuity of a given sense, range of perception, etc. and by developing first an abstract theory of perceiving mechanisms, infer from the values of the determining parameters to the geometrical and physical structure of the sense organ.

As an important parameter we may introduce the degree of differentiation of an organism. Tentatively this may be measured by the average maximum amount M_0 of M that can be removed without destroying the organism as such. We may for instance put for the degree of differentiation D

$$D=\frac{M}{M_0}. \tag{32}$$

While all the above is at this stage meant only as an illustration, even in this crude form the theory suggests a number of new experimental approaches. The relations between M, q, v, n and the length of extremities can be in principle verified experimentally. The same holds of equation (4) and (24). The general conclusions even of this sketchy theory show some overall agreement with actual facts. Thus we see the reason why large flying animals (birds) use only two extremities for running, while smaller ones have six or more. The appearance of four extremities for running in higher developed animals and its reduction to two in the highest, becomes also intelligible. A relation between length of extremities and size of the nervous system suggested twice before from entirely different considerations, now appears in new light. Much is still to be travelled, but the road seems to be clearly indicated.

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